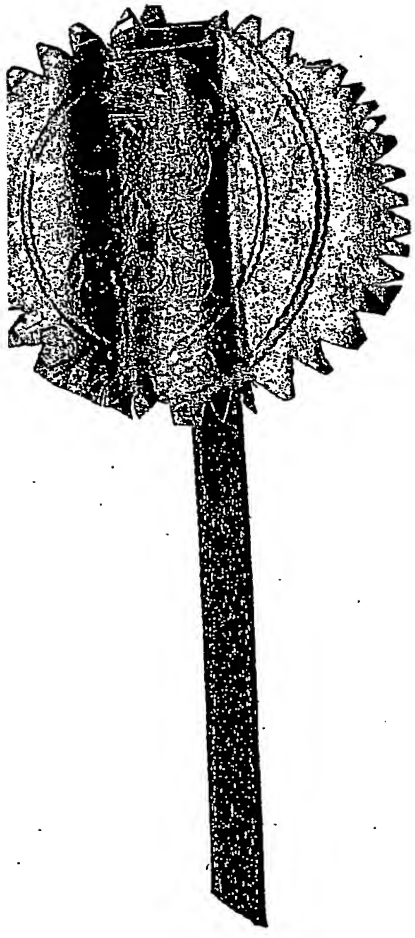
INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

*I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application and Complete Specification filed in connection with Application for Patent No.**447/Del/02** dated **11th April 2002**.*



Witness my hand this 12th Day of May 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

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COMPLIANCE WITH
RULE 17.1(a) OR (b)

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

1047/Del/02
11/4/2002

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled " **A PROCESS FOR THE PREPARATION OF CONTROLLED RELEASE TABLET OF CARBIDOPA / LEVODOPA**"

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. MONA GOGIA
b. RAJEEV S. MATHUR
c. SANJEEV SETHI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Group Leader – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, MONA GOGIA, RAJEEV S. MATHUR, SANJEEV SETHI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Mona Gogia

(MONA GOGIA)

b.

(RAJEEV S. MATHUR)

c. Sanjeev Sethi

(SANJEEV SETHI)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **681010**

dated : **30.03.2002** drawn on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **11TH** day of **April, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR THE PREPARATION OF CONTROLLED RELEASE TABLET OF CARBIDOPA / LEVODOPA

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of controlled release tablet of carbidopa/levodopa comprising a combination of different molecular weight hydroxypropyl cellulose ethers.

Controlled drug delivery applications include both sustained / extended delivery and targeted delivery on a one time or sustained basis. Controlled release formulations can be used to reduce the amount of drug necessary to cause the same therapeutic effect in patients. The convenience of fewer and more effective doses also increases patient compliance.

Parkinson's disease is associated with the depletion of dopamine from cells in the corpus striatum. Since dopamine does not cross the blood brain barrier and cannot therefore be used to treat Parkinson's disease, its immediate precursor, levodopa, is used instead because it penetrates the brain where it is decarboxylated to dopamine. But levodopa is also decarboxylated to dopamine in peripheral tissues and consequently only a small portion of administered levodopa is transported unchanged to the brain. This reaction can be blocked by carbidopa, which inhibits decarboxylation of peripheral levodopa but cannot itself cross the blood brain barrier and has no effect on the metabolism of levodopa in the brain.

The combination of carbidopa and levodopa is considered to be the most effective treatment for symptoms of Parkinson's disease. However, after taking carbidopa/levodopa immediate-release for several years, a patient may find that the effect of the medication begins to wear off before it is time for the next dose. One response is to shorten the intervals between doses (or add an additional dose if needed); another choice is to switch from immediate-release Carbidopa/Levodopa to Controlled Release.

Probably that's why a number of research endeavors have been directed towards preparing a controlled release formulations of carbidopa/ levodopa.

For example, US Pat. No. 4,424,235 discloses hydrodynamically balanced controlled release formulations containing both L-Dopa and a decarboxylase inhibitor. The capsules and tablets are hydrodynamically balanced to have a bulk density (specific gravity) of less than one and therefore, remain floating in gastric fluid, which has a specific gravity of between 1.004 and 1.010. The controlled release formulations described herein comprise

a mixture of the active ingredients with a single polymer selected from a natural gum, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose.. It further contains fatty materials to make the drug flat in the stomach, where the polymer vehicle releases the drug. The dosage form remains buoyant and freely floating in the gastric fluid for an extended period of time during which substantially the entire medicament contained therein is released into the gastric fluid for absorption.

The disadvantage of the floating system is that it must remain buoyant even while absorbing gastric fluid.

The PCT application WO 02/00213 discloses use of non-hydrated hydrogel, super disintegrant and tannic acid to provide gastroretentive dosage form of levodopa. The dosage form expands upon contact with gastric fluid to promote its retention in the patient's stomach for a prolonged period of time and thereby provide sustained release.

The retention of the drug in a tablet or other dosage form beyond the duration of the fed mode raises number of problems that detract from the therapeutic efficacy of the drug. These problems arise from the tendency of the tablet to pass from the stomach into the small intestine, and, thus reaching the colon with the drug still in the tablet, especially when the patient is no longer in the fed mode. This loss of effectiveness occurs with drugs that provide their maximum benefit with minimum side effects when absorbed in the stomach and upper gastrointestinal tract rather than the colon. The reasons are either favorable condition in the stomach, unfavorable conditions in the colon, or both.

To overcome the disadvantages of gastroretentive dosage form, carbidopa/levodopa controlled release dosage forms have been prepared by embedding the active ingredient into a polymer matrix that slowly erodes to release the active. US Pat. Nos. 4,832,957, and 4,900,755 describe a controlled release formulation of levodopa / carbidopa, wherein the desired controlled release is achieved by using a polymer vehicle comprising a combination of water-soluble and less soluble polymers.

The water soluble polymers are selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyethylene glycol, starch, methyl cellulose; whereas less water-soluble polymers are selected from polyvinyl acetate-crotonic acid

copolymer; polyvinyl chloride, polyethylene, cellulose acetate, polyvinyl alcohol, ethylene vinyl acetate copolymer, polyvinyl acetate, polymethyl methacrylate, ethyl cellulose and the like. The preferred polymeric vehicle is the combination of water-soluble polymer, hydroxypropyl cellulose and the less water soluble polymer polyvinyl acetate-crotonic acid.

The invention describes the use of a combination of water soluble and less water-soluble polymers for preparing the control release formulation of carbidopa/levodopa but does not suggest the use of the combination of different molecular weights of single cellulose ether.

US Pat. No. 4,389,393 discloses a formulation for the controlled release of a medicament, using a polymer vehicle that is a combination of hydroxypropyl cellulose and hydroxypropyl methylcellulose. However, it does not suggest the combination of different molecular weights of single cellulose ether.

US Pat. No. 6,103,263 describes use of two types of hydroxypropyl cellulose one of which has a low molecular weight and the other has a high molecular weight to obtain a pharmaceutical formulation having delayed-pulse, sustained release characteristics over at least 12 hour period.

A key disclosure in US Pat. No. 6,103,263 is that the desired sustained release characteristics of the active ingredient can be ensured by 1:1.6 to 1:8.3 and preferably 1:4 ratio of the active ingredient to the mixture of low molecular weight hydroxypropyl cellulose and high molecular weight hydroxypropyl cellulose. It further describes the ratio of low molecular weight hydroxypropyl cellulose to high molecular weight hydroxypropyl cellulose from 1:2 to 1:15. The total polymer content amounts between 24 to 70% weight of the composition.

The higher polymer concentration results in higher cost. Moreover US Pat. No. 6,103,263 does not suggest the use of a combination of low molecular weight hydroxypropyl cellulose and medium molecular weight hydroxypropyl cellulose. US Pat. No. 6,103,263 discloses a dosage form with sustained release characteristics for over at least 12-hour period.

In the present invention we have discovered that a controlled release tablet of carbidopa/levodopa can be prepared using a combination of low and medium molecular

weight hydroxypropyl cellulose ethers, in low concentration. It provides a tablet, which maintains relatively steady plasma levodopa levels for four to six hours.

Therefore, the present invention is directed to a process for the preparation of controlled release tablet of carbidopa/levodopa comprising a combination of low and medium molecular weight hydroxypropyl cellulose in the ratio of 0.75:1 to 1.5:1, wherein the total polymer concentration is up to 20% by weight.

The object of the present invention is to achieve the desired sustained release of carbidopa/levodopa with combination of different molecular weights of single cellulose ether.

Another object of the present invention is to achieve the desired sustained release of carbidopa/levodopa with a combination of low molecular weight hydroxypropyl cellulose and medium molecular weight hydroxypropyl cellulose.

Yet another object of the present invention is to achieve the desired sustained release of carbidopa/levodopa with unusually low concentration of the polymer.

In the present invention these objectives have been accomplished by a process, which comprises blending carbidopa/ levodopa with a blend of two different molecular weight hydroxypropyl cellulose ethers, one of which has low molecular and the other has medium molecular weight; and compressing to make the tablets. Use of low molecular weight or medium molecular weight hydroxypropyl cellulose alone didn't give the desired dissolution profile.

The compositions produced by the present process are quite stable and provide comparable dissolution release profiles vs. the Sinemet® CR (the commercially marketed carbidopa/levodopa controlled release tablets). As the present process employs low concentration of the polymer, cost of the production is considerably reduced.

For the present invention, carbidopa may be used between 5-300 mg, whereas levodopa may be used in between 20-1200 mg.

Hydroxypropyl cellulose of present invention is the combination of low and medium molecular weights hydroxypropyl cellulose. Low molecular weight hydroxypropyl cellulose may be selected from hydroxypropyl cellulose having a number average molecular weight of 55,000 and 70,000, whereas medium molecular weight hydroxypropyl cellulose may be selected from hydroxypropyl cellulose having a number average molecular weight of 1,10,000 to 1,50,000. However combination of hydroxypropyl cellulose having a number average molecular weight of about 65,000 and about 1,25,000 is most preferred. A combination of different molecular weight hydroxypropyl methylcellulose may also be used.

The concentration of the combination of low and medium molecular weight hydroxypropyl cellulose normally may vary up to 20% by weight of the total composition. However from the finding of the present invention (as shown in the examples), it was discovered that the preferred range is between 2% to 20 % w/w.

The ratio of low molecular weight hydroxypropyl cellulose to medium molecular weight hydroxypropyl cellulose may vary from 0.75:1 to 1.5:1. However ratio of about 1:1 is preferred.

In addition to the active and hydroxypropyl cellulose, the formulation of the present invention may contain additives or excipients which act in one or more capacities as diluents, binders, disintegrants, lubricants, glidants, colorants or flavoring agents.

Lactose, mannitol, sucrose, microcrystalline cellulose, starches and calcium hydrogen phosphate may be used as diluent.

Disintegrants may be selected from croscarmellose sodium, crospovidone and sodium starch glycolate.

Binders impart cohesiveness to the blend and also improve the flow and hardness. In the present invention excipients like starch, sugars, gums and povidone may be used as binders.

Lubricants of the present invention may be selected from talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium lauryl sulphate, sodium stearyl fumarate and sodium benzoate.

Glidants may be selected from Colloidal silicon dioxide, aerosil or talc.

Suitable coloring or flavoring agent includes those approved for use by the United States Food and Drug Administration (FDA) and are well known to those skilled in the art.

The tablets of the present invention may be prepared by dry blending levodopa, carbidopa with combination of low molecular weight hydroxypropyl cellulose and medium molecular weight hydroxypropyl cellulose; wet granulating the blend with aqueous solution of binder; drying and sizing the wet granules; and compressing the granules.

Alternatively direct compression or dry granulation techniques may be used to prepare tablets, however wet granulation is preferred.

The tablets can be optionally coated using the standard coating processes.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention anyway.

In the following examples the carbidopa levodopa tablets were prepared using the process of the present invention and employing polymer between 2 - 20% w/w of the total composition.

Examples 1- 8

Ingredient	Examples (concentration-Mg per tablet)							
	1	2	3	4	5	6	7	8
Carbidopa	54.91	59.28	54.91	54.91	54.91	54.91	54.39	54.94
Levodopa	201.35	201.35	201.35	201.35	201.35	201.35	201.73	201.73
Diluent	50.515	26.35	5.04	8.04	10.04	20.04	12.88	9.64
Hydroxypropyl cellulose- L	15.0	25.0	15	15	12.5	7.5	12.5	12.5
Hydroxypropyl cellulose -M	20.0	30.0	15	12	12.5	7.5	10	12.5
Povidone K-30	3.5	3.5	3	3	3	3	3	3
Iron oxide red	0.35	0.35	0.2	0.2	0.2	0.2	0.25	0.3
D & C yellow no. 10	0.875	0.875	0.5	0.5	0.5	0.5	0.25	0.4
solvent	q.s.	q.s.	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3.5	3.5	5	5	5	5	5	5

Process:

1. Weigh and sift all excipients for the batch.
2. Prepare a solution of Povidone in water/aqueous alcohol/ alcohol.
3. Blend Carbidopa, Levodopa, with Hydroxypropyl cellulose and colorants and granulate the blend with Povidone solution.
4. Dry and size the granules; and blend with magnesium stearate.
5. Compress into tablets.

The controlled release tablets prepared according to the above examples provide sustained release of carbidopa & Levodopa up to 2.5 hours. The dissolution profile clearly shows that 0.75:1 - 1.5:1 ratio of low to medium molecular weight hydroxypropyl cellulose provides the similar extended release as Sinemet® CR. Moreover, the desired release of carbidopa levodopa can be achieved using the low concentration of hydroxypropyl cellulose.

Table 1 provides the comparative dissolution of the controlled release tablets of carbidopa/ levodopa prepared by the composition and process of examples (1-8) vs. the marketed sample Sinemet ® CR in 0.1N HCl (900 ml), USP 2 at 50 rpm.

Table 1

Comparative dissolution of the controlled release tablets of Carbidopa levodopa prepared as per Examples 1- 8 vs Sinemet® CR in 0.1N HCl (900 ml), USP 2 at 50 rpm.

Time (h)	% drug released																	
	Ex. 1		Ex. 2		Ex. 3		Ex. 4		Ex. 5		Ex. 6		Ex. 7		Ex. 8		Sinemet® CR	
	C	L	C	L	C	L	C	L	C	L	C	L	C	L	C	L	C	L
0.5	36	35	27	26	36	38	37	38	31	31	29	34	33	35	31	34	33	35
1.0	68	66	50	48	54	57	60	63	53	52	54	55	65	69	57	59	59	61
1.5	89	87	74	70	75	79	78	81	-	-	-	-	-	-	-	-	-	-
2.0	101	99	91	86	87	92	87	92	-	-	-	-	-	-	-	-	-	-
2.5	107	106	104	97	98	103	95	100	98	96	97	95	103	108	93	96	97	98

- C- Carbidopa
- L- Levodopa

WE CLAIM:

1. A process for the preparation of controlled release tablet of carbidopa/levodopa comprising a combination of different molecular weight hydroxypropyl cellulose ethers.

2. The process according to claim 1 wherein the hydroxypropyl cellulose ethers are the combination of low and medium molecular weight hydroxypropyl cellulose ethers.

3. The process according to claim 2 wherein the low molecular weight hydroxypropyl cellulose is selected from hydroxypropyl cellulose having a number average molecular weight of 55,000 and 70,000.

4. The process according to claim 3 wherein the low molecular weight hydroxypropyl cellulose has a number average molecular weight of about 65,000.

5. The process according to claim 2 wherein the medium molecular weight hydroxypropyl cellulose is selected from hydroxypropyl cellulose having a number average molecular weight of 1,10,000 to 1,50,000.

6. The process according to claim 5 wherein the medium molecular weight hydroxypropyl cellulose has a number average molecular weight of about 1,25,000.

7. The process according to claim 2 wherein the ratio of low molecular weight hydroxypropyl cellulose to medium molecular weight hydroxypropyl cellulose is between 0.75:1 to 1.5:1.

8. The process according to claim 7 wherein the ratio of low molecular weight hydroxypropyl cellulose to medium molecular weight hydroxypropyl cellulose is 1:1.

9. The process according to claim 1 wherein the total hydroxypropyl cellulose concentration is between 2 - 20% w/w.

10. The process according to claim 1 wherein hydroxypropyl cellulose is replaced with hydroxypropyl methylcellulose.

11. The process according to claim 1 wherein the tablet comprises other excipients in addition to carbidopa, levodopa and hydroxypropyl cellulose ether.

12. The process according to claim 11 wherein the said other excipients are selected from diluents, binders, disintegrants, lubricants, glidants, colorants and flavoring agents.

13. The process according to claim 1 wherein the tablets are prepared by wet granulation, dry granulation or direct compression.

14. The process according to claim 13 wherein the wet granulation is done with aqueous or hydro-alcoholic or alcoholic dispersion of the binder.

15. The process according to claim 1 wherein tablet provides drug release up to 2.5 hours.

16. A process for preparing controlled release tablets containing carbidopa/ levodopa substantially as described and illustrated by the examples herein.

Dated this **11TH** day of **April, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary